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Comparison of Cyanoacrylate Tissue Adhesives to Polytetrafluoroethylene Sutures in the Donor Site of Connective Tissue Grafts – A Randomized Clinical Trial

MDent (Periodontics)

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Comparison of Cyanoacrylate Tissue Adhesives to Polytetrafluoroethylene (PTFE) Sutures in the Donor Site of Connective Tissue Grafts - A Randomized Clinical Trial

Abstract

Purpose: The aim of this study was to compare patient-centered outcomes, wound healing and post-operative complications at palatal donor area of SECT grafts between cyanoacrylates tissue adhesives and Polytetrafluoroethylene (PTFE) sutures.

Methods: 36 patients who required harvesting of SECT graft were enrolled in this prospective randomized clinical trial and assigned to one of two groups. In the "suture" group, wound closure was achieved with standardized continuous interlocking 6-0 PTFE sutures, while in the "cyanoacrylate" group, a high viscosity blend of n-butyl and 2-octyl cyanoacrylate was applied until hemostasis was achieved. The primary outcome was the discomfort (eating, speaking etc) from the donor site during the first post-operative week; this was self-reported on a visual analogue scale (VAS) questionnaire. Secondary outcomes were the time required for suture placement or cyanoacrylate application, the patient self-reported pain on the first day, and the first week after surgery, the analgesic-intake and the modified early-wound healing index (MEHI).

Results: The median value of discomfort was 1.49 cm in the "suture" group and 1.86 cm in the "cyanoacrylate" (p=0.56). The mean time required for suture placement was 7.31 minutes and for cyanoacrylate application 2.16 minutes (p<0.0001). No statistically significant differences were found between the two methods in reported level of pain, in analgesic intake and in MEHI.

Conclusion: Cyanoacrylate can safely be used for wound closure of donor palatal site of SCTG. The application was about 5 minutes faster than conventional suture placement, reducing the total time of the surgical procedure.

Key words: cyanoacrylates, sutures, wound healing, tissue grafts, clinical trial

1. INTRODUCTION

Subepithelial connective tissue (SECT) grafts are considered the "gold standard" treatment in periodontal plastic surgery[1]. SECT graft procedures require harvesting tissue from a donor area, usually the palate[2]. This addition of another surgical site extends the complexity of the procedure and increases patient discomfort[2]. Horizontal suspension[3] or continuous interlocking[2] sutures are the most common method of wound closure[4]. The difficulty with suturing and the need for suture removal are major challenges; therefore, research has focused on more effective wound closure methods with better efficiency and fewer complications[4]. Biomaterials such as staples, adhesive tapes, cyanoacrylate tissue adhesives, and fibrin sealants have been used generally to accelerate healing[5].

Cyanoacrylate adhesives are synthesized as monomers by condensation of a cyanoacetate with formaldehyde in the presence of catalysts and the adhesive film develops by fast polymerization triggered by hydroxyl groups on the surfaces to be glued[6]. The reaction of polymerization is exothermic; does not require catalysts, solvents, or application pressure; and leads to strong and flexible bonds[6,7]. Water can act as a catalyst to activate this anionic polymerization[8]. Cyanoacrylate adhesives retain their adhesive qualities even in the presence of moisture, and have the added benefits of being bacteriostatic and hemostatic[8]. Their general chemical formula is CH2=C(CN)-COOR , where R can be substituted for any alkyl group, ranging from methyl to decyl[5,6,7,9]. Methyl cyanoacrylate, the shortest-chain derivative, was the first glue developed, but tissue toxicity precluded its use[5,10]. Longer-chain derivatives such as ethyl-2-cyanoacrylate, isobutyl-2-cyanoacrylate, butyl-2-cyanoacrylate, n-butyl cyanoacrylate and 2-octyl-cyanoacrylate have subsequently been developed[9]. Changing the type of alkyl chains in

the compound to one with a longer molecular chain can reduce tissue toxicity[9]. The properties of cyanoacrylate tissue adhesives with the greatest interest in the surgical field are the reported excellent hemostasis, rapid adhesion of tissues, and possible bacteriostatic qualities[6]. Their use in dentistry is restricted to superficial application[7].

Few studies are focused on evaluating wound healing and assessing patient-centered outcomes on the palatal donor area following different harvesting techniques[2,11]. To the best of our knowledge, there is no study that compares different methods of wound closure of the donor site in SECT graft procedures. The aim of this study was to compare patient-centered outcomes, post-operative complications, and wound healing at palatal donor areas between those receiving sutures and cyanoacrylate tissue adhesives.

2. MATERIALS AND METHODS

2.1 Patient population and enrollment

The trial was approved by the University of Manitoba's Biomedical Research Ethics Board (HS20114 (B2016:092) and registered on ClinicalTrials.gov (NCT02935426). Patients attending the Dr. Sam Borden Periodontology Clinic, Dr. Gerald Niznick College of Dentistry, University of Manitoba requiring harvesting of SECT graft from the palate from January 2017 to April 2018 and had signed the consent form were included in the study. Patients received an initial periodontal examination and treatment, if necessary. Full Mouth Plaque Score and Full Mouth Bleeding Score needed to be <20% to be eligible. Patients with coagulation disorders (Hemophilia a/b, von Willebrand disease, liver disease, anticoagulative therapy), patients on corticosteroids, with uncontrolled diabetes, or with any systemic disease that precluded

periodontal surgery, as well as patients with a history of contact dermatitis to formaldehyde were excluded from the trial.

2.2 Surgical protocol

The surgical procedures were performed by one of three calibrated periodontics residents (CS, JB, DR). The three surgeons were calibrated in a calibration meeting using the detailed parameters from the study protocol and clinical pictures. For all measurements the same periodontal probe[*] was used.

At the donor site, anesthesia was achieved with greater palatine block anesthesia and palatal local infiltrations, if needed, with 1.8ml Lidocaine 2% 1: 100,000 epinephrine. The thickness of the palatal gingiva at the donor site was measured with bone sounding. The SECT grafts were harvested with the single incision technique[12]. Once the graft was harvested pressure was applied to the palate until hemostasis was achieved. The thickness, length, and height of the harvested graft were measured with a periodontal probe and recorded.

2.3 Wound closure groups

The participants were then randomly assigned to one of two groups, the suture or the cyanoacrylate group. Block-randomization for each of the three operators was achieved using a computerized randomization scheme. In the suture group, continuous interlocking 6-0 Polytetrafluoroethylene (PTFE) sutures[†] were placed 4mm apart[2] leaving 3-4mm tails. In the cyanoacrylate group, thin layers of a high viscosity blend of n-butyl and 2-octyl – cyanoacrylate

[*] Hu-Friedy PCPUNC 15mm, Hu-Friedy, Chicago IL, USA
[†] Omnia 6/0, 75 cm PTFE Surgical Suture with 1/2 circle Diamond Tip needle, Omnia LLC, Abbottstown, PA, USA

tissue adhesive[‡] were applied and rinsed with saline at least 3 times with an interval of at least 30 seconds[13] to allow for complete polymerization, until hemostasis was achieved. The number of sutures placed and the number of layers of cyanoacrylate applied to achieve hemostasis were recorded. The time required for suture placement or for cyanoacrylate application was also recorded with a timer.

All participants received a loading dose of Amoxicillin 2gr or Clindamycin 600mg, in case of allergy to penicillin, and Ibuprofen 400mg immediately after the surgery. All patients received the same post-operative instructions. Soft diet was recommended for all participants. Chlorhexidine 0.12% mouth rinse was prescribed to each patient for use twice daily. Ibuprofen 200mg, 20 tablets were also dispensed for the participants to consume 1-2 tablets orally every 4-6 hours as needed. Participants were asked to return the unused tables for recording of analgesic-intake at the 1-week follow-up appointment. A 10cm pain visual analogue scale (VAS) questionnaire was given to the participants to note the level of pain from the palatal site on the first post-operative day, before the consumption of analgesics.

2.4 Post-operative records

Post-operative complications like severe bleeding, infection, abnormal pain, root exposure of the teeth adjacent to the donor site, and sloughing were recorded for 1 month post-operatively.

At the 1-week follow-up appointment, analgesic-intake during the first post-operative week was recorded. Participants were asked to report any self-medication for pain. A 10cm VAS questionnaire was also given to participants to fill in. The participants were asked to note the

[‡] PeriAcryl®90 High Viscosity, GluStitch Inc., Delta, BC, Canada

level of pain from the donor and recipient sites, and the level of discomfort (eating, speaking, etc.) from the donor site during the first post-operative week. Sutures were removed in the suture group. The length and height of the wound at the palatal site were measured with a periodontal probe and recorded. The modified early-wound healing index (MEHI)[2] (Figure 1) and the presence of normal or abnormal inflammation were recorded.

2.5 Statistical analysis

According to the sample size calculation[§], 32 subjects with 16 participants in each group were required, anticipating 1cm standard deviation[2]. In total 36 subjects were recruited in the trial to allow for 10% drop-outs or losses to follow-up and for balance among the operators. The primary outcome was the discomfort from the donor site during the first post-operative week. Secondary outcomes were the time required for suture placement or cyanoacrylate application, the level of pain from the palatal site on the first post-operative day and during the first post-operative week, the analgesic-intake, and the MEHI. The study was blinded at the level of data assessment.

Mean, median, minimum, maximum values, and standard deviations for all records were analyzed for each group. For comparing continuous outcomes between the two methods of wound closure, the Wilcoxon rank sum test was used. For the discrete outcome of MEHI, the Fisher exact test was used. The null hypothesis was that the two methods are the same, and the alternative that they differ. The level of significance was established at p=0.05.

3. RESULTS

[§] stat.ubc.ca

Data from 35 subjects, 18 subjects in the suture group and 17 subjects in the cyanoacrylate group, were available at the end for analysis. Out of the initially 36 recruited subjects in the study, one participant from the cyanoacrylate group failed to attend on the day of the surgery for unknown reasons and no records were collected. One participant in the cyanoacrylate group was a smoker and one participant in the suture group reported smoking cannabis. Both participants were encouraged to cease smoking during the healing period. Out of the 35 subjects, 23 had significant medical history. The reported conditions are presented in Table 1. The subject with the allergy to Ibuprofen received Acetaminophen 1gr and 20 tabs of Acetaminophen 500mg to consume as needed during the first post-operative week. There were 10 males and 25 females, aged 23 to 81 years, included in the study. The demographic characteristics of the study population are presented in Table 2. In the same table (Table 2), the summary from the data on the thickness of the palate, the length of the incision, the thickness, height and length of graft, and the number of sutures placed or the number of cyanoacrylate coats applied are presented.

There were no major imbalances between the two wound closure methods with respect to age, thickness of palate, length of incision, thickness of graft, height of graft or length of graft. However, groups were noticeably different in their gender profiles.

Regarding the primary outcome, the level of discomfort from the palate during the first post-operative week (Figure 2A), the mean value for the suture group was 1.49cm $\pm$ 1.96 on the VAS and for the cyanoacrylate group 1.86cm $\pm$ 2.25 (Table 3). The difference between the two groups was not statistically significant (p=0.56).

With regards to the time required for suturing or application of the cyanoacrylate adhesive (Figure 2B), the mean value for the suture group was 7.31 minutes $\pm$ 2.19 and for the cyanoacrylate group 2.16 minutes $\pm$ 1.21 (Table 3). The difference between the two methods of wound closure was 5.15 minutes (p<0.0001).

For the level of pain reported from the palate on the first post-operative day (Figure 2C), the mean value for the suture group was 1.42cm $\pm$ 1.88 and for the cyanoacrylate 1.27cm $\pm$ 1.92 (p=0.96) (Table 3). As far as the level of pain from the palate during the first post-operative week (Picture 2D), the mean value for the suture group was 1.07cm $\pm$ 1.87 and for the cyanoacrylate group 1.55cm $\pm$ 2.32 (p=0.28) (Table 3). For the analgesic-intake during the first post-operative week (Figure 2E), the median value for the suture and the cyanoacrylate group was 4 tablets of Ibuprofen 200mg (p=0.94). Figure 2E reveals that the cyanoacrylate group demonstrated a bi-modal distribution, comprised of two distinct groups, whereas the suture group was more of a single continuum. Self-medication was reported by 11 out of the 35 participants, 5 from the suture group and 6 from the cyanoacrylate group. Three of these participants reported Ibuprofen intake and the number of tablets consumed were added to the analgesic intake. For the remainder of the subjects, there were no records on the type and the number of analgesics consumed.

For the MEHI, we were forced to combined categories 1 with 2 and 4 with 5 due to the small sample size. The results for the MEHI are presented on Table 4. The difference between the two methods of wound closure was no statistically significant (p=0.91).

Post-operative bleeding was reported from 2 participants in the cyanoacrylate group. In the first subject, the bleeding occurred during the second post-operative week and lasted 15

minutes. It was managed with tongue pressure. The patient did not notify the operator of the incident and just reported it at the second follow-up appointment. The incident may be related to the incorrect application of the adhesive. In the second subject, the bleeding occurred during the first post-operative week after consumption of fruits and lasted about 4 minutes. The patient was reassured and no further management was required.

Abnormal inflammation was recorded only for one subject. Necrosis and edema at the palatal site were noted without signs of infection at the 1-week follow-up appointment. No specific management was required. MEHI 5 was assigned to this patient. The healing was completed uneventfully. The level of pain and discomfort reported from the patient was at the area of 0.5cm and the patient took only 1 tablet of Ibuprofen during the first week of healing.

From additional analysis, it was found that the MEHI did not correlate with the dimensions of the graft (length, height, or thickness). The dimensions of the graft were also not related to the analgesic-intake or to the level of reported pain. Finally, no significant relationship was found between the MEHI and analgesic-intake or the reported pain.

4. DISCUSSION

In this randomized clinical trial, clinical outcomes from two different methods of wound closure of the palatal donor site of connective tissue grafts were compared. Continuous interlocking 6-0 PTFE sutures or application of a high viscosity blend of n-butyl and 2-octyl–cyanoacrylate tissue adhesive was randomly selected as a wound closure method in 35 participants after harvesting SECT graft with the single-incision technique[12]. No significant differences were found between the two methods in terms of patient discomfort and post-operative pain. The two methods also demonstrated similar wound healing, as evaluated with the MEHI. Highly significant difference

between the two groups was found only in the time required for suture placement or cyanoacrylate application.

The application of cyanoacrylate tissue adhesive in the donor palatal site of SECT graft was found to be more than 3 times faster than suture placement. Soni et al. found that the time savings increased for cyanoacrylate as the length of the incisions increased, because the application time, unlike that of sutures, does not increase significantly with incision size[14].

The single-incision technique for harvesting of SECT grafts results in less secondary wound healing, minimum patient discomfort and limited post-operative complications compared to other techniques[2,3,12]. For these reasons, this technique was chosen in our study.

Continuous interlocking 6-0 PTFE sutures were selected for wound closure in the suture group as used from Fickl et al.[2]. As a monofilament, PTFE does not accumulate plaque enhancing wound healing. It is also non-resorbable, minimizing the risk of early loss and post-operative bleeding.

There were no major imbalances between the two methods of wound closure with respect to age, thickness of the palatal gingiva, length of the incision, thickness of the harvested graft, height or length of the graft. Therefore, these are unlikely to confound the association between method of wound closure and the outcomes of pain, MEHI and time. However, the groups were noticeably different in their gender profile. The increased total number of females in the study is in agreement with the results of Furuta et al.[15]. However, randomization should have brought gender balance between the two groups. The imbalance may be due to the small sample size. If gender is associated with any of the outcomes, this may bias the results. For this reason, we tested for associations between gender and each of the following outcomes; patient

discomfort, time, pain on the first post-operative day and during the first post-operative week, analgesic-intake, and MEHI. None of them were significant, except for gender and time. However, time is the only outcome that differs between the two methods. In a regression model (data not included), the relationship between method of wound closure and time remained highly significant upon adjustment for gender, and both the magnitude and direction of the relationship were largely unchanged.

10cm VAS questionnaires were elected to evaluate the level of pain and discomfort in our study. Because pain is a subjective, personal and private experience recording pain has limitations[16]. The VAS is considered to be an efficacious tool to evaluate clinical parameters, such as pain[4,14], especially for pain assessment after surgery[16].

Post-operative bleeding was reported only from two participants in this study. The first incident occurred during the second post-operative week and may be related to the incorrect application of the cyanoacrylate adhesive. The second incident occurred after consumption of food. This is in agreement with Griffin et al., that bleeding is associated with postoperative irritation or trauma, rather than the surgical procedure[17].

The cyanoacrylate tissue adhesive used in the study is a blend of n-butyl cyanoacrylate and 2-octyl cyanoacrylate. Butyl cyanoacrylate is a bacteriostatic, biodegradable, hemostatic cyanoacrylate with a long half-life and good tissue compatibility[10]. It sets within 5-10 seconds by polymerization in the presence of moisture and even blood, with release of heat[10]. The octyl cyanoacrylate is more elastic demonstrating higher breaking strength allowing the application in higher tension wounds[5,7]. In a systematic review, the high viscosity adhesives were found to be less time-consuming to use than low viscosity ones, but the time difference was small[18].

Tissue adhesion occurs by valence bonding and van der Waal's force[10]. The bond strength depends on the morphology of the tissue site as well as the preparation of the surfaces to be bonded (i.e. approximation)[13]. Prior to the application of cyanoacrylate, the tissue surfaces should be cleaned and dried as much as possible. Careful application drop by drop is better than rapid massive application, to minimize heat production during polymerization[9]. A mean temperature increase of 1.5°C was recorded for butyl-2-cyanoacrylate[19]. After its application, tissues should be immobilized for 30 seconds for completion of polymerization[20].

Immediate permanent hemostasis can be achieved after application of cyanoacrylate tissue adhesives[6,7,20]. The mechanism by which cyanoacrylate glues achieve hemostasis is not clear. The hypothesis is that the ester forms a macrofilm causing mechanical blockage to slow blood flow, providing a surface agent to activate the clotting cascade[13].

Degradation occurs by breaking of the double carbon bond and elimination from the body through urine and faeces[10]. The adhesive is sloughed from the surface by 5 days, and the remnants of cyanoacrylate are phagocytosed[21]. The histotoxic effect is related to the heat of polymerization, the byproducts of the polymer degradation such as formaldehyde and alkyl cyanoacetate, the length of the alkyl group of cyanoacrylate derivatives and the rate at which degradation occurs[7,9,14]. The derivatives with short alkyl side chain elicit a severe inflammatory response that causes tissue necrosis[6,7,22,23]. Longer chain cyanoacrylates evoke only mild transient inflammation and demonstrate low cytotoxicity[6,7,9,23] because they are depredated more slowly than the short-chain cyanoacrylate[22,23]. The inflammatory reaction to cyanoacrylate is caused by dependent reactions of the tissue oxygen[24]. Foreign body reaction with histiocytic proliferation[25] and formation of giant cells in tissues[26] has been reported

histologically on cyanoacrylate sites. Kulkarni et al. reported less inflammation clinically and histologically at 7 days after the use of cyanoacrylate tissue adhesive for closure of periodontal flap as compared to sutures[10]. The difference disappeared at 21 days and at 6 weeks[10]. Giant cell proliferation or histiocytes were not reported in either of the sites of that study[10]. Bhasker and Frisch said that there would be giant cell reaction and phagocytosis if the cyanoacrylate material were to be implanted deep into the tissue[27]. Thus, the cyanoacrylate adhesives should be topically applied after the edges of the incision are brought together, to avoid entrapment of adhesive within the wound[5]. If the polymer was accidentally swallowed, degradation, and assimilation of a significant percentage of the polymer occurred in an animal model with rats[28]. There is no evidence of carcinogenesis of isobutyl- and butyl-2-cyanoacrylate[14].

Dermatologic reactions, such as urticarial reactions and irritant dermatitis and other non-dermatologic reactions (reversible eye and upper airway irritation) have been reported from cyanoacrylate adhesives[29]. Outbreaks of asthma and irritant dermatitis in dental staff were observed where the environmental humidity was low[29]. The high levels of humidity are thought to induce polymerization of free monomers of cyanoacrylates, thereby reducing their volatility reactions[29]. Dental staff should take care to avoid direct contact with cyanoacrylate, use cyanoacrylate in a well-ventilated area, and wear appropriate personal protective equipment[29].

Similar wound healing was found between sutures and cyanoacrylate tissue adhesives in this study. However, cyanoacrylates have been shown to speed wound healing in partial-thickness wounds in an animal model[30]. In contrast with our results, cyanoacrylate adhesives were found to aid in early initial healing and cause less intraoperative and postoperative discomfort to patients after application on intraoral wounds, as compared with standard suture

wound closure[5]. Perez et al. found high patient acceptance of tissue adhesives because of pain relief and less eating discomfort[20].

No signs of infection were noted on any of the participants. Cyanoacrylate adhesives have antimicrobial properties against gram-positive organisms and may decrease wound infections[31]. The antibacterial effect is possibly caused by strong electronegative charge of the polymer[32].

Ghoreishian et al. reported that the use of cyanoacrylate adhesives for wound closure after removal of impacted mandibular third molars was characterized by simplicity, higher speed, and better hemostasis[4]. However, they considered the cost of tissue adhesive to be a limitation[4]. In our study, it was calculated that the PTFE sutures were three times more expensive than the cyanoacrylate adhesive. Other disadvantages reported are the occasional difficulty of application at posterior sites, especially palatally and lingually, and the ease with which the monomer will polymerize on exposure to small amounts of moisture[6].

Potential limitations in this clinical trial include the lack of a negative control group for ethical reasons and to avoid excess post-operative bleeding, the blindness only at the level of data analysis, and the noticeable imbalance in the gender profile of the two treatment groups. Moreover, the possible variation in the thickness of the overlying flap and the thickness of the graft, the varying amounts of areas harboring the palatal blood clot, the multiple surgeons and the second surgical site may be seen as limitations of this study. Even though the two groups were balanced and no significant relationship was found, it cannot be ruled out that the varying flap/graft dimensions and varying surgeons may have influenced the healing capacity, thus patient discomfort and pain post-operatively. Furthermore, the duration of the soft tissue grafting procedure is an important indicator for post-operative pain[11]. Also, differences in

patient perception can also influence the levels of reported post-operative pain[11,33]. Thus, caution is needed in interpreting our results, as this clinical trial may be affected by an unintentional bias. Even though efforts were made to increase compliance with returning the pain questionnaires and unused tablets of Ibuprofen during the first week of healing, a few participants returned them at the second follow-up appointment. This can be considered a limitation of this study. Finally, the sample size was too small to detect any differences in healing between the two methods of wound closure.

5. CONCLUSION

From this randomized clinical trial, it can be concluded that cyanoacrylate tissue adhesives can safely be used for wound closure of the palatal donor site of SECT grafts. The application of cyanoacrylate tissue adhesive was more than 3 times faster than the placement of sutures. No statistically significant differences were found between the two methods of wound closure in terms of patient discomfort and post-operative pain.

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REFERENCES

1. Chambrone L, Tatakis DN. Periodontal soft tissue root coverage procedures: a systematic review from the AAP Regeneration Workshop. *J Periodontol* 2015; 8(2) :S8-51
2. Fickl S, Fisher K, Jockel-Schneider Y et al. Early wound healing and patient morbidity after single-incision vs. trap-door graft harvesting from the palate – a clinical study. *Clin Oral Investig* 2014; 18 :2213-2219
3. Hurzeler W. A single-incision technique to harvest subepithelial connective tissue grafts from the palate. *Int J Periodontics Restorative Dent* 1999; 19(3) :279-287
4. Ghoreishian M, Gheisari R, Fayazi M. Tissue adhesive and suturing for closure of the surgical wound after removal of impacted mandibular third molars: a comparative study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 108 :e14-e16
5. Vastani A, Maria A. Healing of intraoral wounds closed using silk sutures and isoamyl-2-cyanoacrylate glue: a comparative clinical and histologic study. *J Oral Maxillofac Surg* 2013; 71 :241-248
6. Forrest JO. The use of cyanoacrylates in periodontal surgery. *J Periodontol* 1974; 45(4) :225-229
7. Herod EL. Cyanoacrylates in dentistry: a review of the literature. *J Can Dent Assoc* 1990;56(4) :331-334
8. Leggat P, Kedjarune U, Smith DR. Toxicity of cyanoacrylate adhesives and their occupational impacts for dental staff. *Ind Health* 2004;42 :207-211
9. Toriumi DM, Raslan WF, Friedman M et al. Histotoxicity of cyanoacrylate tissue adhesives. *Arch Otolaryngol Head Neck Surg* 1990; 116 :546-550

10. Julkarni S, Dodwad V, Chava V. Healing of periodontal flap when closed with silk sutures and N-butyl cyanoacrylate: a clinical and histological study. *Indian J Dent Res* 2007;18(2) :72-77
11. Pandit N, Khasa M, Gugnani S et al. Comparison of two techniques of harvesting connective tissue and its effects on healing pattern at palate and recession coverage at recipient site. *Contemp Clin Dent* 2016; 7(1) : 3-10
12. Lorenzana E, Allen E. The single-incision palatal harvest technique: a strategy for esthetics and patient comfort. *Int J Periodontics Restorative Dent* 2000; 20 : 297-305
13. Al-Belasy F, Amer MZ. Hemostatic effect of n-butyl-2-cyanoacrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. *J Oral Maxillofac Surg* 2003; 61 :1405-1409
14. Soni A, Narula R, Kumar A et al. Comparing cyanoacrylate tissue adhesive and conventional subcutical skin sutures for maxillofacial incisions – a prospective randomized trial considering closure time, wound morbidity and cosmetic outcome. *J Oral Maxillofac Surg* 2013; 71 :2152.e1-2152.e8
15. Furuta M, Ekuni D, Irie K et al. Gender differences in gingivitis relate to interaction of oral health behaviors in young people. *J Periodontol* 2011;82(4) : 558-565
16. Breivik H, Borchgrevink PC, Allen SM et al. Assessment of pain. *Br J Anaesth* 2008; 101(1) : 17-24
17. Griffin TJ, Cheung WS, Zarvas AI et al. Postoperative complications following gingival augmentation procedures. *J Periodontol* 2006; 77 :2070-9

18. Dumville JC, Coulthard P, Worthington HV et al. Tissue adhesives for closure of surgical incision (review). *Cochrane Database Syst Rev* 2014; 11
19. Hida T, Sheta SM, Proia AD et al. Retina toxicity of cyanoacrylate tissue adhesive in the rabbit. *Retina* 1988; 8 :148-153
20. Perez M, Fernandez I, Marquez D et al. Use of n-butyl-2-cyanoacrylate in oral surgey: biological and clinical evaluation. *Artif Organs* 2000; 24(3) :241-243
21. Galil KA, Schofield ID, Wright GZ. Effect of n-butyl-2-cyanoacrylate (histoacryl blue) on the healing of skin wounds. *J Can Dent Assoc* 1984; 7 :565
22. Ronis ML, Harwick JD, Fung R et al. Review of cyanoacrylate tissue glues with emphasis on their otorhinolaryngological applications. *Laryngoscope* 1984;94 :210-213
23. Fung RQ, Ronis ML, Mogr RM. Use of butyl-2-cyanoacrylate in rabbit auricular cartilage. *Arch Otolaryngol* 1985; 111 :459-464
24. Zabeu Rossi Costa HJ, Pereira CSB, Costa MP et al. Experimental comparative study in rabbits of three different ways of cartilage graft fixation: suture, gelatin-resorcin-formaldehyde and butyl=2-cyanoacrylate. *Acta Otolaryngol* 2009; 127(9) :947-951
25. Greer R. Studies concerning the histotoxicity of isobutyl-2-cyanoacrylate tissue adhesive when employed as an oral hemostat. *Oral Surg* 1975; 40 :659-69
26. Miller GM, Dannenbaum R, Cohen WD. A preliminary histologic study of the wound healing of mucogingival flaps when secured with cyanoacrylate tissue adhesives. *J Periodontol* 1974; 45 :608-18
27. Bhasker SN, Frisch J. Use of cyanoacrylate adhesives in dentistry. *J Am Dent Assoc* 1968; 77 : 831-7

28. Ousterhout DK, Gladieux GV, Wade CW et al. Digestive tract absorption of alkyl α-cyanoacrylate-β-14C. *Oral Surg Oral Med Oral Pathol* 1969; 27 :410
29. Yoo J, Chandarana S, Cosby R. Clinical application of tissue adhesives in soft-tissue surgery of the head and neck. *Curr Opin Otolaryngol Head Neck Surg* 2008;16 :312-317
30. Davis SC, Eaglestein WH, Cazzaniga AL et al. An octyl-2-cyanoacrylate formulation speeds healing of partial-thickness wounds. *Dermatol Surg* 2001; 27 : 783-788
31. Quinn JV, Ramotar K, Osmond MH. The antimicrobial effects of a new tissue adhesive. *Acad Emerg Med* 1996; 3 :536-537
32. Quinn J, Maw J, Ramotar K et al. Octylacrylate tissue adhesive versus suture wound repair in a contaminated wound model. *Surgery* 1997;122 :69-72
33. Gilman T. Wound outcomes: the utility of surface measures. *Int J Low Extrem Wounds* 2004;3 :125-32

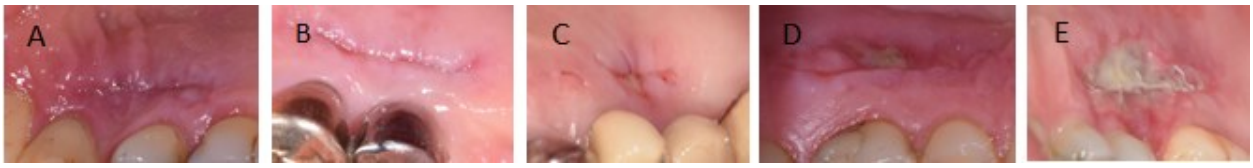

***Figure 1**. Modified early wound healing index (MEHI); **1A.** MEHI 1: complete flap closure without fibrin line at the palate; **1B.** MEHI 2: complete flap closure with fibrin line at the palate; **1C.** MEHI 3: complete flap closure with small fibrin clot at the palate; **1D.** MEHI 4: incomplete flap closure with partial necrosis of the palatal tissue; **1E.** MEHI 5: incomplete flap closure with complete necrosis of the palatal tissue (> 50% of former flap)*

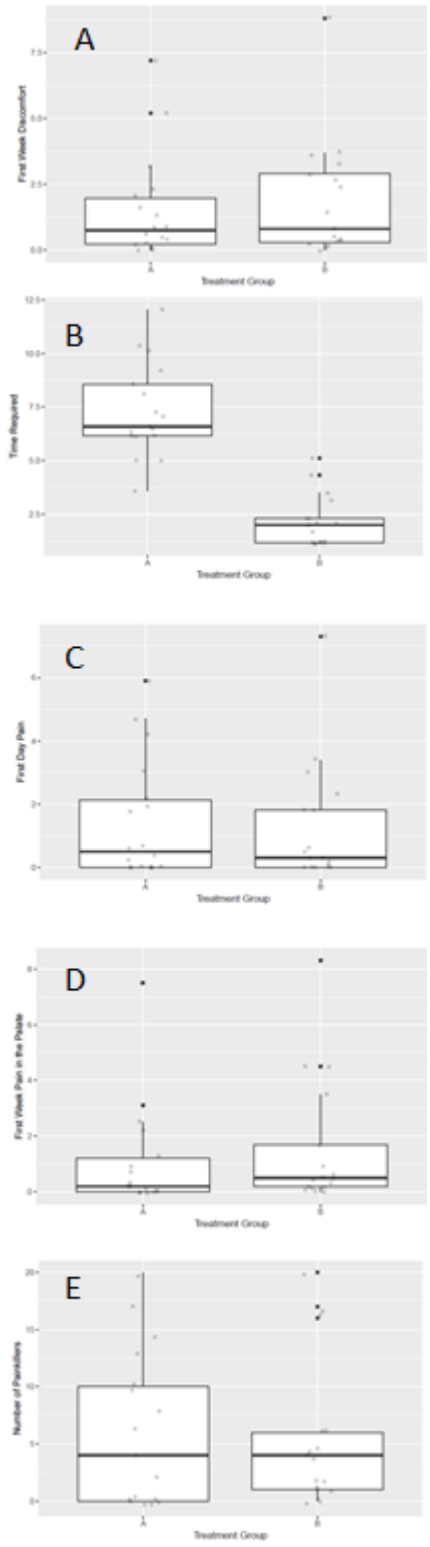

Figure 2. *Graphs comparing treatment groups;* ***2A.*** *First week of discomfort, p=0.56;* ***2B.*** *Time, p<0.0001;* ***2C.****Pain_first day, p=0.96;* ***2D.*** *Pain_first week, p=0.28;* ***2E.*** *Analgesic-intake, p=0.94; group A: sutures, group B: cyanoacrylate*

Table 1. *List of medical conditions reported*

Table 1. Reported medical conditions	
Controlled hypothyroidism	Restless leg syndrome
Asthma	Inflammatory bowel disease
Arthritis	Hepatitis B
Controlled hypertension	Herpes simplex virus-2 infection
Fibromyalgia	History of breast cancer
Hypercholesterolemia	Use of recreational drugs
Acid reflex	Allergy to Amoxicillin
Controlled diabetes	Allergy to Gabapentin
Depression	Allergy to Ibuprofen

Table 2. *Summary of results for age, sex, thickness of palate, length of incision, thickness, height and length of graft and number of sutures or layers of cyanoacrylate; Group A: sutures, Group B: cyanoacrylate*

Table 2. Summary of results from baseline records		
	Group A	Group B
Age (years)	58.5; min: 23, max: 74 (SD: 13.52)	53.18; min: 27, max: 81 (SD: 20.2)
Gender	9 females, 9 males	16 females, 1 male
Thickness palate (mm)	3.44; min: 2, max: 5 (SD: 0.77)	3.38; min: 2, max: 5 (SD: 0.78)
Length incision (mm)	18.94; min: 15, max: 25 (SD: 2.78)	17.06; min: 10, max: 31 (SD: 5.51)
Thickness graft (mm)	2.14; min: 1.5, max: 3 (SD: 0.36)	2.41; min: 2, max: 3 (SD: 0.51)
Height graft (mm)	7.03; min: 3, max: 20 (SD: 4.83)	6.41; min: 4, max: 14 (SD: 2.67)
Length graft (mm)	15.06; min: 4, max: 24 (SD: 4.26)	13.76; min: 6, max: 27 (SD: 6.42)
Sutures/layers #	6.67; min: 5, max: 8 (SD: 0.97)	4.41; min: 3, max: 8 (SD: 1.23)

Table 3. *Summary of results for discomfort, time, pain and analgesic-intake; Group A: sutures, Group B: cyanoacrylate*

Table 3. Summary of results for primary and secondary outcomes					
Outcomes	Mean (min – max, SD)		Median		*p*-value
	Group A	Group B	Group A	Group B	
Discomfort (cm)	1.49 (0 - 7.2, 1.96)	1.87 (0 - 8.8, 2.25)	0.75	0.80	0.56

Time (min)	7.31 (3.57 - 12.06, 2.19)	2.16 (1.12 - 5.11, 1.21)	6.59	2.00	<0.0001
Pain_first day (cm)	1.42 (0 - 5.9, 1.88)	1.27 (0 - 7.3, 1.92)	0.5	0.3	0.96
Pain_first week (cm)	1.07 (0 - 7.5, 1.87)	1.55 (0 - 8.3, 2.32)	0.2	0.5	0.28
Analgesic intake	6.12 (0 – 20, 6.79)	5.24 (0 – 20, 6.30)	4	4	0.94

Table 4. *Summary of results for the Modified-Early Wound Healing Index (MEHI)*

Table 4. Summary of results for MEHI			
Category	Group A	Group B	*p*-value
MEHI 1 or 2	44.4%	35.3%	0.91
MEHI 3	16.7%	23.5%	
MEHI 4 or 5	38.9%	41.2%	